

*For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR
for Specialist Use only*

Xbira 250 mg

Abiraterone Acetate Tablet USP 250mg

Composition

Each tablet contains.

Abiraterone acetate USP..... 250 mg

Excipient with known effect: Lactose

Dosage Form

Uncoated Tablet

Product Description

White to off-white oval shaped tablets, debossed with “A” on one side and “250” on other side

Excipients

Povidone, Sodium Lauryl Sulfate, Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Purified water, Colloidal silicon dioxide, Magnesium stearate

Pharmacology

Pharmacodynamics

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17 α -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17 α -hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition

also results in increased mineralocorticoid production by the adrenals (see *Warnings and Precautions*).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer.

Pharmacokinetics

Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see *Pharmacodynamics*).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold ($C_{\max}$) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in highly variable exposures. Therefore, abiraterone must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone. The tablets should be swallowed whole with water (see *Dosage and Method of Administration*).

Distribution

The plasma protein binding of ^{14}C -abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5,630 l, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

Following oral administration of ^{14}C -abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43% of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours. Following oral administration of ^{14}C -abiraterone acetate 1,000 mg, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Hepatic impairment

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.

The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (see *Dosage and Method of Administration* and *Warnings and Precautions*). Abiraterone acetate should not be used in patients with severe hepatic impairment (see *Dosage and Method of Administration*, *Contraindications* and *Warnings and Precautions*).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see *Dosage and Method of Administration* and *Warnings and Precautions*).

Renal impairment

Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis. Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction (see *Dosage and Method of Administration*). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Indications

Abiraterone is indicated with prednisone or prednisolone for

- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.
- the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Abiraterone is also indicated in combination with prednisone or prednisolone and androgen deprivation therapy (ADT) for the treatment of patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) who may have received up to 3 months of prior ADT.

Dosage and Method of Administration

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology

The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see “*Method of administration*” below). Taking the tablets with food increases systemic exposure to abiraterone (see *Drug Interactions and Pharmacokinetics*).

Dosage of prednisone or prednisolone

For mCRPC, Abiraterone is used with 10mg prednisone or prednisolone daily.

For mHSPC, Abiraterone is used with 5mg prednisone or prednisolone daily.

Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

Recommended monitoring

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a

significant risk for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see *Warnings and Precautions*).

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with abiraterone, consider maintaining the patient's potassium level at ≥ 4.0 mM.

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with abiraterone should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

In the event of a missed daily dose of either abiraterone, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately (see *Warnings and Precautions*). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablet) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued.

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated

Hepatic impairment

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A. Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately four-fold following single oral doses of abiraterone acetate 1,000 mg (see *Pharmacokinetics*). There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of abiraterone should be cautiously

assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see *Dosage and Method of Administration* and *Pharmacokinetics*). Abiraterone should not be used in patients with severe hepatic impairment (see *Contraindications, Warnings and Precautions* and *Pharmacokinetics*)

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see *Pharmacokinetics*). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see *Warnings and Precautions*).

Paediatric population

There is no relevant use of abiraterone in the paediatric population.

Method of administration

Abiraterone is to be administered orally. The tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. These should be swallowed whole with water.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Women who are or may potentially be pregnant (see *Fertility, Pregnancy and Lactation*).
- Severe hepatic impairment [Child-Pugh Class C (see *Dosage and Method of Administration, Warnings and Precautions* and *Pharmacokinetics*)].

Warnings and Precautions

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess

Abiraterone may cause hypertension, hypokalaemia and fluid retention (see *Undesirable Effects*) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see *Pharmacodynamics*). Co-administration of a corticosteroid suppresses adrenocorticotrophic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose

underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

Before treating patients with a significant risk for congestive heart failure (e.g. a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function (e.g. echocardiogram). Before treatment with abiraterone, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with abiraterone treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function (see *Dosage and Method of Administration*).

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred. (see *Undesirable Effects*). Serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If at any time the ALT or AST rises above 5 times the upper limit of normal (ULN) or the bilirubin rises above 3 times ULN, treatment should be interrupted immediately and liver function closely monitored.. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see *Dosage and Method of Administration*).

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be re-treated with abiraterone

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of abiraterone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see *Dosage and Method of*

Administration and Pharmacokinetics). Abiraterone should not be used in patients with severe hepatic impairment (see *Dosage and Method of Administration, Contraindications and Pharmacokinetics*).

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of abiraterone in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole

Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Hypoglycaemia

Cases of hypoglycaemia have been reported when Xbira was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes.

Use with chemotherapy

The safety and efficacy of concomitant use of abiraterone with cytotoxic chemotherapy has not been established

Intolerance to excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Potential risks

Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with abiraterone.

Skeletal muscle effects

Cases of myopathy have been reported in patients treated with abiraterone. Some patients had rhabdomyolysis with renal failure. Most cases developed within the first month of treatment and recovered after abiraterone withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see *Drug Interactions*).

Drug Interactions

Effect of food on abiraterone acetate

Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety when given with food have not been established therefore this medicinal product must not be taken with food (see *Dosage and Method of Administration* and *Pharmacokinetics*).

Interactions with other medicinal products

Potential for other medicinal products to affect abiraterone exposures

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

Co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential to affect exposures to other medicinal products

Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide.

Use with products known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with abiraterone is not recommended (see *Pharmacodynamics*).

Fertility, Pregnancy and lactation

Women of childbearing potential

There are no human data on the use of abiraterone in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females

It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity.

Pregnancy

Abiraterone is not for use in women and is contraindicated in women who are or may potentially be pregnant (see *Contraindications*).

Lactation

Abiraterone is not for use in women.

Fertility

Abiraterone affected fertility in male and female rats, but these effects were fully reversible.

Undesirable effects

Summary of the safety profile

Adverse reactions that were observed were peripheral oedema, hypokalaemia, hypertension urinary tract infection, and alanine aminotransferase increased and/or aspartate aminotransferase increased.

Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

Abiraterone may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see *Warnings and Precautions*).

Tabulated list of adverse reactions

Metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone (10mg)

Frequency categories are defined as follows: very common, common, uncommon, rare, very rare and not known

Table 1: Adverse reactions	
System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see <i>Warnings and Precautions</i> and <i>Drug Interactions</i>)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis ^a
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia

Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased ^b rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash
Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**
* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased ** Fractures includes osteoporosis and all fractures with the exception of pathological fractures ^a Spontaneous reports from post-marketing experience ^b Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.	

Overdose

Human experience of overdose with abiraterone is limited.

There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

Incompatibilities

Not applicable.

Shelf-Life

24 months

Storage and Handling Instruction

Store below 30°C. Protect from light

Packaging Information

120 Tablets packed in 150cc HDPE Round Opaque white/off-white bottles

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